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(54) Title: TARGETED TUMOR THERAPY BY USE OF RECOMBINANT ADENOVIRUS VECTORS THAT SELECTIVELY REPLICATE IN HYPOXIC REGIONS OF TUMORS

(57) Abstract: The presently claimed subject matter provides conditionally replication competent adenoviral vectors that confer selective cytotoxicity on cells expressing HIF-1 by infecting cells that allow HIF-1 inducible promoters present within the vectors to function. Also provided are compositions and host cells based upon the vectors, as well as methods of propagating and using the vectors. The presently claimed subject matter further provides a method of inhibiting tumor growth by co-infecting cells in a tumor with a conditionally replication competent adenovirus vector in conjunction with a replication deficient adenovirus vector.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/31097

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 48/00; C12N 5/10, 15/86, 15/861
US CL : 435/320.1, 325, 455, 456, 457, 465; 424/93.2; 514/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/320.1, 325, 455, 456, 457, 465; 424/93.2; 514/44

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/26192 A2 (EMORY UNIVERSITY) 04 April 2002(04.04.2002), see entire reference, especially pages 7-9, 13-14, 17-20, 22-24, 27-35, 37-40.	1-23
Y		24-36
X	US 2001/0053352 A1 (YU et al.) 20 December 2001 (20.12.2001), see entire reference, especially paragraphs 0018-0034, 0044-0047, 0085, 0089, 0090, 0092, 0094, 0096-0098, 0102, 0105, 0112, 0113, 0139-0144, 0154-0163, 0170, claims 1-10, 17-25, 27 and 28.	1-3, 9-23
Y		4-8, 24-36
X	HERNANDEZ-ALCOCEBA et al. New oncolytic adenoviruses with hypoxia- and estrogen receptor-regulated replication. Human Gene Therapy. 20 September 2002, Vol. 13, No. 14, pages 1737-1750, see entire reference, especially pages 1737, 1738, 1740, 1742, 1746, 1747.	1-3, 9, 10, 15-18, 21-23
Y		6-8, 11-14, 24-35
P, X	POST et al. A novel hypoxia-inducible factor (HIF) activated oncolytic adenovirus for cancer therapy. Oncogene. 10 April 2003, Vol. 22, No. 14, pages 2065-2075, see entire reference.	1-12, 15-18, 20-23
Y		13, 14

☒ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

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"&" document member of the same patent family

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C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X — P, Y	HUANG et al. A hypoxia-selective oncolytic adenovirus for cancer therapy. International Journal of Radiation Oncology, Biology, Physics. 06 October 2002, Vol. 54, No. 2 Supplement, page 122, Abstract 205.	1-3, 6, 9, 10, 15-18, 20-22 4, 5, 7, 8, 19, 23
Y	SHIBATA et al. Development of a hypoxia-responsive vector for tumor-specific gene therapy. Gene Therapy. March 2000, Vol. 7, No. 6, pages 493-498, see entire reference.	4-8
A	BOSHART et al. A very strong enhancer is located upstream of an immediate early gene of human cytomegalovirus. Cell. June 1985, Vol. 41, pages 521-530, see Fig.3A, nucleotides -53 to +7.	4, 5
A	SHIBATA et al. Enhancement of gene expression under hypoxic conditions using fragments of the human vascular endothelial growth factor and the erythropoietin genes. International Journal of Radiation Oncology, Biology, Physics. 01 November 1998, Vol. 42, No. 4, pages 913-916, see page 914, column 1.	6-8
A	LIU et al. Hypoxia regulates vascular endothelial growth factor gene expression in endothelial cells. Circulation Research. September 1995, Vol. 77, No. 3, pages 638-643, see Figure 4, sequence "A-G".	6-8
Y	WO 98/35028 A2 (BAXTER INTERNATIONAL INC.) 13 August 1998 (13.08.1998), see entire reference, especially pages 8-14, 17-21, 23-35, 29, 30	24-36

INTERNATIONAL SEARCH REPORT

PCT/US03/31097

Continuation of B. FIELDS SEARCHED Item 3:

USPT, PGPB, DWPI, MEDLINE, EMBASE, BIOSIS, CAPLUS, SCISEARCH, GENBANK, EMBL, GENESEQ
search terms: adenovir?, hypox?, hre, oncolytic, condition? replicat?, Dewhirst M?